DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 6 2001

David Jespersen
L. Perrigo Company
Director of Technical Affairs
515 Eastern Avenue
Allegan, Michigan 49010

Re: Docket No. 98N-0337
Comment Nos. APP11 & APP12

Dear Mr. Jespersen:

This letter is in response to your Applications for Exemption (coded APP 11 & APP 12), dated October 6, 2000, submitted under 21 C.F.R. § 201.66(e), for L. Perrigo Company (Perrigo) Day Time Liquid-Filled Capsules (Perrigo product code 389) and Suphedrine Cough & Cold Liquid-Filled Capsules (Perrigo product code 80).

Your application requests an exemption from the labeling requirements for over-the-counter (OTC) drug products set forth in 21 C.F.R. § 201.66(c)(8) regarding the listing of inactive ingredients. You state that your company purchases the Day Time Liquid-Filled Capsules and Suphedrine Cough & Cold Liquid-Filled Capsules from two manufacturers whose formulations contain identical active ingredients with different inactive ingredients, specifically, different color additives. You state that requiring separate labels is impracticable when an OTC drug manufacturer uses multiple suppliers because it would require Perrigo to maintain an inventory of separate labeling for each supplier, which would be costly. You claim that there would be a significant business risk to have only one manufacturer source the product in the event that there is a supply problem. You also state that you cannot direct suppliers to manufacture from a single formula because it would place an undue and, in some cases, impossible burden on the manufacturer.

You note in your Applications for Exemption that prior to passage of the Food and Drug Administration Modernization Act of 1997 (FDAMA), it was industry practice to use "may contain" or "may also contain" in the inactive ingredient labeling section to indicate those inactive ingredients that differed between multiple suppliers of the same product. You note that this approach would not affect the safety and efficacy of the product.

As you recognize, FDAMA amended § 502(e)(1)(A) of the Act, creating a requirement that inactive ingredients be listed in alphabetical order on the outside retail package of OTC drug products. The new provision in subclause (iii) states that a drug is misbranded unless its label bears:

> the established name of each inactive ingredient listed in alphabetical order on the outside container of the retail package and, if determined to be appropriate by the Secretary, on the immediate container, as prescribed in regulation promulgated by the Secretary, except that nothing in this subclause shall be deemed to require that any trade secret be divulged, and except that the requirements of this subclause

with respect to alphabetical order shall apply only to nonprescription drugs that are not intended for human use.

Today, the Food and Drug Administration (FDA) also responded to two citizen petitions requesting FDA to amend 21 C.F.R. § 201.66 to allow an OTC drug manufacturer to use the phrase "may contain" or "may also contain" in the inactive ingredient section of the finished drug product labeling. (Copies of the citizen petition responses are enclosed.) FDA responded affirmatively, in principle, to the requests, with modifications, noting that the agency does not believe that the language or legislative history of § 502(e)(1)(A) of the Federal Food, Drug, and Cosmetic Act (the Act), as well as agency precedent, precludes an over-inclusive listing of inactive ingredients that are in or possibly in an OTC drug product in alphabetical order on its labeling.[1] Additionally, nothing in 21 C.F.R.§ 201.66(c)(8), or § 201.66 in general, would preclude this type of listing either. Consequently, FDA does not believe that companies have to submit Applications for Exemption under 21 C.F.R.§ 201.66(e) in order to list certain inactive ingredients, that may or may not be present in the product, in the inactive ingredients section of the "Drug Facts" box.

In the citizen petition responses, FDA notes that because § 502(e)(1)(A)(iii) of the Act requires inactive ingredients to be listed in alphabetical order, use of "may contain" or "may also contain" labeling, in the manner specifically requested in your citizen petition would, as a practical matter, most likely violate the Act. This is because it may be impossible for those alternative ingredients following the "may contain" clause to maintain an alphabetical order. FDA, however, believes that over-inclusive inactive ingredient labeling may be accomplished consistent with the Act by placing those ingredients that may or may not be contained in the OTC drug product in the inactive ingredient listing, as set forth in 21 C.F.R. § 201.66(c)(8), with an asterisk placed next to those ingredients.[2] The asterisk would then be reprinted at the end or bottom of the inactive ingredient section of the "Drug Facts" box, with the notation "contains one or more of these ingredients." [3,4]

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[1] FDA uses the term "over-inclusive inactive ingredient labeling" to generally describe labeling statements identifying ingredients that may or may not be present in a particular product.

[2] For example: "*acacia, *dextrose, sucrose, *xanthum gum" or "acacia*, dextrose*, sucrose, xanthum gum*". FDA may issue future guidance on labeling formats and other issues related to matters discussed in this letter.

[3] For example, for product labeling that uses the standard format set forth in § 201.66, left justify the statement at the end of the inactive ingredient section: "*contains one or more of these ingredients". For product labeling that uses the modified format set forth in § 201.66(d)(10), the statement should appear at the end of the inactive ingredient section with 2 square "ems" between last inactive ingredient listed and the statement "*contains one or more of these ingredients". See § 201.66(d)(4). FDA may issue future guidance on labeling formats and other issues related to matters discussed in this letter.

[4] FDA views the phrase "contains one or more of these ingredients" preferable to the phrase "may contain" or "may also contain." The latter type of over-inclusive inactive ingredient labeling has the potential to mislead consumers, in that such statements do not advise whether any of the ingredients following the statement definitively appear in the product. On the other hand, "contains one or more" informs the consumer that at least one of the alternative ingredients referred to by the phrase is present in the product.

FDA intends to issue guidance to the industry listing suggested parameters for the use of the inactive ingredient asterisk listing. Such parameters may include limiting the number of ingredients associated with the asterisk, limiting the type of ingredients associated with the asterisk, including the optional information in 21 C.F.R. § 201.66(c)(9) ("Questions?" or "Questions or comments?" followed by the telephone number of a source to answer questions about the product,) and a reminder to follow all applicable current good manufacturing practice for finished pharmaceuticals regulations in 21 C.F.R. part 211 so that manufacturers have appropriate records of which lot numbers of the product contain which inactive ingredients. The guidance also may contain direction regarding the graphical placement and size of the asterisk and related statement.

According to your Applications for Exemption, Day Time Liquid-Filled Capsules and Suphedrine Cough & Cold Liquid-Filled Capsules contain FD&C Yellow No. 6. Agency regulations in 21 C.F.R. § 201.20(c) discuss specific declaration of the presence of FD&C Yellow No. 6 in the labeling of OTC drug products intended for human use administered orally, nasally, rectally, or vaginally. In the Federal Register of December 6, 1988 (53 FR 49138), this requirement was suspended pending further agency action. In the Federal Register of July 21, 1995 (60 FR 37611), the agency proposed that the suspension of the effective date of 21 C.F.R. § 201.20(c) be removed. The agency is in the process of finalizing the 1995 proposal.

If and when the agency finalizes the proposed rule requiring specific declaration of FD&C Yellow Dye No. 6, Day Time Liquid-Filled Capsules and Suphedrine Cough & Cold Liquid-Filled Capsules would not be able to take advantage of the asterisk listing for inactive ingredients. If the agency determines that for public health and safety reasons consumers must affirmatively know whether FD&C Yellow No. 6 is or is not in the product, this ingredient would be unsuitable to be listed with an asterisk next to it.

Be advised that our review of your exemption requests do not constitute a full labeling review of these products. The labeling for these products continue to be subject to all applicable labeling requirements in 21 C.F.R. § 201.66, and any other applicable regulations.

If you have any questions, please contact Walter Ellenberg, Ph.D., Regulatory Health Project Manager, at 301-827-2222.

Sincerely yours,

Charles J. Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research